# Neurobehavioral Effects of Developmental Methylmercury Exposure


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Methylmercury (MeHg) is a global environmental problem and is listed by the International Program of Chemical Safety as one of the six most dangerous chemicals in the world's environment. Human exposure to MeHg primarily occurs through the consumption of contaminated food such as fish, although catastrophic exposures due to industrial pollution have occurred. The fetus is particularly sensitive to MeHg exposure and adverse effects on infant development have been associated with levels of exposure that result in few, if any, signs of maternal clinical illness or toxicity. High levels of prenatal exposure in humans result in neurobehavioral effects such as cerebral palsy and severe mental retardation. Prenatal exposure to MeHg in communities with chronic low-level exposure is related to decreased birthweight and early sensorimotor dysfunction such as delayed onset of walking. Neurobehavioral alterations have also been documented in studies with nonhuman primates and rodents. Available information on the developmental neurotoxic effects of MeHg, particularly the neurobehavioral effects, indicates that the fetus and infant are more sensitive to adverse effects of MeHg. It is therefore recommended that pregnant women and women of childbearing age be strongly advised to limit their exposure to potential sources of MeHg. Based on results from human and animal studies on the developmental neurotoxic effects of methylmercury, the accepted reference dose should be lowered to 0.025 to 0.06 MeHg μg/kg/day. Continued research on the neurotoxic effects associated with low level developmental exposure is needed. — Environ Health Perspect 103(Suppl 6):135–142 (1995)



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## Introduction

It is well established that prenatal exposure to certain toxic chemicals can have profound and irreversible effects on the physical and mental development of children. Of agents known to act as toxicants, those that cause central nervous system damage (neurotoxicants) constitute a particularly significant public health hazard. While episodes of high-dose neurotoxicant exposure to children have shown clear evidence of neurological disorders, the more subtle action of moderate to low-dose neurotoxicant exposure on important parameters of behavioral development is increasingly evident (*1–3*). Laboratory-based research and documented incidents of human exposure to neurotoxicants such as lead, alcohol, and methylmercury (MeHg) point to a continuum of effects in exposed children ranging from subtle behavioral changes to frank expression of neurological damage and death. In general, the long-term consequences of developmental exposure to neurotoxicants are only now beginning to receive scientific attention.

Although there are a number of important neurotoxicants, this article focuses on the effects of developmental exposure to MeHg, a prevalent environmental contaminant. The serious public health concerns associated with MeHg exposure have resulted in world-wide attention, research, and review (*4–14*). The aim of this article is to provide an updated overview of the developmental effects of MeHg exposure, reexamine currently recommended exposure guidelines, and highlight future research needs.

In recognition of the adverse effects of MeHg exposure, state and federal government agencies and international agencies have developed recommendations to limit MeHg exposure. For example, the U.S. Food and Drug Administration (U.S. FDA) recommends a limit of 1 μg/g (1 ppm) mercury in the edible portion of fish. The U.S. Environmental Protection Agency (U.S. EPA) has established a reference dose (RfD) for methylmercury at 0.3 μg/kg/day, which is equivalent to consumption of 19 μg per day of MeHg for a 62-kg woman (*15*). The RfD is defined as an estimate of a daily exposure to a human population that is likely to be without an appreciable risk of deleterious effects during a life time and is meant to include sensitive subgroups. The RfD typically is arrived at through standard risk assessment procedures that include a careful evaluation of study results, determination of the lowest observed adverse effect level (LOAEL) dose, and division of the LOAEL by an appropriate uncertainty factor to yield a RfD. The World Health Organization (WHO) does not use the RfD nomenclature but developed a similar recommendation that is equivalent to 0.47 μg/kg/day in adults (*16*) while noting that pregnant women, nursing mothers, and their infants are likely to be at greater risk. A recent reevaluation of the RfD for MeHg was done by Stern (*14*), who concluded that the RfD should be lowered to 0.07 μg/kg/day based on human and animal studies on developmental effects of MeHg. Upon review of the human and animal literature, the authors of the current review reached a similar conclusion.

## Mercury Contamination — Methylmercury Exposure

Mercury is generally released into the environment in an inorganic form by both natural and anthropogenic sources (*4,11,16, 17*). Natural sources of mercury include emissions from volcanoes, degassing of the earth's crust, and evaporation from water.


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Artificial sources of mercury include industrial pollution, burning of fossil fuels, mining, refuse incineration, and cremation. Natural emissions of mercury into the atmosphere have been estimated to range from 2700 to 6000 metric tons per year, while world wide mining of mercury is estimated to yield 10,000 tons per year (*4*). It is estimated that human activities result in the release of 3000 tons per year of mercury. A significant source of environmental mercury contamination is gold mining in countries such as in Brazil (*18,19*). Mercury release due to gold mining results in environmental contamination through direct effluent discharge into local waterways and through volatilization (*18*). Approximately 3 to 5 kg of mercury are used to extract 1 kg of gold, of which 25 to 45% is lost during the amalgamation process (*20*). Atmospheric mercury undergoes photochemical oxidation and is then scavenged by atmospheric particulates or precipitation. Global contamination occurs as the mercury is washed out of the atmosphere onto soil, vegetation, and water (*4,21*).

The majority of environmental MeHg contamination has occurred through the biotransformation of inorganic mercury to organic mercury (MeHg) in a process termed methylation. During methylation, inorganic mercury is converted into MeHg by microbial action, primarily in sediments of fresh and ocean waters. Methylmercury readily enters the aquatic food chain and is biomagnified as it accumulates in predatory fish such as swordfish, pike, and ocean tuna. Larger and more long-lived fish tend to contain more MeHg. Methylmercury contamination in fish can be significant; for example, the total mercury in the edible tissues of shark and swordfish can average as high as 1200 µg/kg (*16*). Marine mammal and fish consumption, while not the only sources of MeHg exposure, are extremely important routes of human exposure. This is particularly true for populations depending on fish as a primary food source.

Methylmercury is readily absorbed and distributed throughout the body, including the brain. In humans, MeHg brain levels are approximately six times higher than blood mercury levels (*22*). This is in contrast to rats, which have a brain-to-blood ratio of 0.06, and mice with a ratio of 1.20. These differences in brain MeHg accumulation have important implications for the extrapolation of human health guidelines from animal data. Methylmercury also readily crosses the placenta and appears to accumulate in the fetus so that fetal mercury levels are greater than maternal blood mercury levels (*23*). The differential accumulation of MeHg in the brain and the fetus are important factors in defining developmental MeHg neurotoxicity.

## Fetal Sensitivity to Methylmercury Exposure

Methylmercury is an excellent example of a known neurotoxicant that is also a prevalent and dangerous environmental pollutant. The effects of *in utero* exposure to MeHg are quite different from the effects associated with childhood or adult exposure (*16*). The fetus is more sensitive to the toxic effects of MeHg and severe effects have been found in the offspring of women showing little or no overt evidence of MeHg exposure (*24–26*). Catastrophic exposures in both Japan and Iraq provided evidence that mercury-exposed women delivered infants with severe behavioral and sensory deficits, including deafness and blindness, without expressing significant clinical signs or symptoms of mercury toxicity during pregnancy.

On both biological and neurobehavioral levels, there is strong evidence of fetal sensitivity to MeHg. Prenatal exposure to MeHg appears to result in a widespread pattern of adverse effects on brain development and organization (*13,16,27–29*) . This generalized pattern of MeHg-induced injury to fetal brains is not seen in the adult brain, where MeHg exposure is characterized by localized lesions at specific neural sites (*30*). Postmortem studies from epidemic exposures in Japan and Iraq have revealed that MeHg significantly alters the normal migration of neurons to the cerebellar and cerebral cortices during brain development (*27,28*).

Examination of the brains of infants and animals exposed to MeHg *in utero* has revealed changes in neuronal migration and distribution patterns, cell loss (low neuronal abundance), and reduced brain size and gliosis (*27,29,31,32*). Hypotheses explaining MeHg-mediated developmental neurotoxicity include changes in intracellular cytoskeletal structure (*33–35*), oxidative stress (*36–38*), alterations to membrane function and signal transduction (*39*), decreased protein production (*40*), and changes in neurotransmission (*41*).

## Neurobehavioral Effects in Human Infants

The disruptive effects of in utero MeHg exposure on brain development have been associated with a broad range of neurobehavioral alterations in infancy and childhood. Published reports of studies involving mothers and infants come primarily from Japan, Iraq, Canada, and New Zealand. There are, however, additional reports of mother–infant pairs under study in the Seychelles Islands, Greenland, and the Faroe Islands (Table 1). Methylmercury exposure is usually estimated by blood or hair mercury levels, and it is generally accepted that the hair mercury concentration is 250 times that of the blood (*16*).

The catastrophic human exposures that occurred in Minamata and Niigata, Japan in the 1950s established that MeHg was fetotoxic (*26,42*). In the Minamata Bay study, 23 children believed to have been exposed to MeHg *in utero* showed evidence of mental retardation and cerebral palsy. During pregnancy, levels of Hg exposure were not monitored in the mothers of these children, but as a group these women showed little clinical evidence of MeHg toxicity. More subtle neurobehavioral deficits were not systematically studied in Japan; however, a general assessment of IQ in elementary and junior high-school students in the Minamata school district and a control district did not reveal any large differences in group performance (*16*). In the city of Minamata, a separate study found a significant correlation between level of MeHg in umbilical cord blood and occurrence of mental retardation (*16*).

In Iraq, an investigation of 29 mother–infant pairs was initiated after a serious outbreak of MeHg poisoning from consumption of contaminated bread (*43*). Results indicated a significant relationship between prenatal MeHg exposure and infant psychomotor retardation. Clear evidence of delays in attaining developmental milestones (e.g., motor and speech retardation) were evident in children with maternal hair MeHg levels less than 180 ppm. Neurological symptoms such as increased muscle tone and exaggerated deep tendon reflexes were primarily associated with maternal hair MeHg levels higher than 180 ppm. A subsequent report detailed the results of 84 mother–infant pairs (including the 29 discussed above), with peak maternal hair levels ranging from 0.4 to 640 ppm (*44*). Severe neurological symptoms (e.g., blindness, deafness, failure to walk, talk, or stand by over 4.5 years) were documented in five children. The lowest peak maternal hair level associated with severe neurological problems was 165 ppm (range 165–320 ppm). These reports were the first to docu-

**Table 1.** Human developmental effects of *in utero* exposure to MeHg.

| Geographic location | Maternal MeHg exposure | Neurobehavioral effects | References |
|---|---|---|---|
| Japan | In Minamata, maternal samples taken 2 to 5 years after fetal delivery were elevated<br>In Niigata, one mother had hair mercury levels of 293 ppm during pregnancy | Cerebral palsy, mental retardation, limb deformities, visual disorders, delayed speech, ataxia | Harada (*26,42*) |
| Iraq | Severe neurological deficits, with peak hair mercury concentrations from 165 to 320 ppm<br>Mild deficits between 68 and 180 ppm | Mental and motor retardation, cerebral palsy, seizures, delayed speech, blindness, deafness | Marsh et al. (*44*) |
| Greenland | Mean blood value of 38.1 ppb | Reduced birth weight | Foldspang and Hansen (*56*) |
| Faroe Islands | Mean cord blood of 24.2 ppb<br>Over 25% greater than 40 ppb | Neurobehavioral data not yet available | Grandjean et al. (*57*)<br>Grandjean and Weihe (*58*) |
| New Zealand | Blood levels during pregnancy range from 6 to 86 ppb | Early sensorimotor deficits such as retarded walking, decreased scores on developmental tests | Kjellstrom et al. (*53*)<br>Kjellstrom et al. (*54*) |
| Canada | Mean cord blood of 6 ppb; maternal hair 6 ppm | Abnormal deep tendon reflex in male infants | McKeown et al. (*48*) |

ment more subtle impairments in children exposed to lower levels of MeHg during gestation and suggested a continuum of MeHg-related effects closely linked to maternal dose. Data from Iraq were reevaluated in an effort to determine a dose–response relationship between maternal hair levels of mercury and developmental effects (*45*). From this analysis, it was concluded that delayed onset of walking may occur at maternal hair levels of 10 to 20 ppm, which is equivalent to maternal blood mercury levels of 40 to 80 ppb.

The Iraq episode provided an opportunity for systematic follow-up of MeHg-exposed infants and children (*46,47*). Standard clinical and neurological tests including the Gesell Developmental Screening Exam were used as neurobehavioral assessment measures. Offspring effects ranged from hyperreflexia and delayed motor activity to microcephaly, cerebral palsy, and death. Follow-up studies at approximately 5 years of age indicated significant delays in psychomotor development and persistent pathological reflexes in a substantial number of children who did not display clinical signs during infancy. The clinical diagnoses of these children resembled minimal brain dysfunction (MBD) syndrome.

In Canada, a study of prenatal MeHg exposure in 234 Cree Indian infants and children did not find strong evidence of developmental abnormalities (*48*). Anthropometric measurements, neurological exams, and the Denver Developmental Scales were used as test measures with the children. The mean maternal hair level in this study was 6 ppm. No effects on physical development were noted for either males or females. Significant neurobehavioral effects were limited to the finding that maternal exposure to MeHg was related to abnormal muscle tone (deep tendon reflex) in male infants. No effects of exposure to MeHg were noted in female infants and the authors note the questionable clinical significance of this sex-specific finding. Animal data, however, would suggest that there may be sex-related effects of prenatal MeHg exposure, with males generally showing a greater sensitivity to *in utero* exposure (*29,49–52*) .

Studies of children prenatally exposed to MeHg through maternal fish consumption have been conducted in New Zealand (*53*). Approximately 1000 women were identified as frequent fish consumers and of these, 73 were identified as having maternal hair concentrations above 6 ppm (range 6–86 ppm). At 4 years of age, 31 offspring from this group were assessed with the Denver Developmental Screening Test. Evidence of a significant increase in the risk of early sensorimotor dysfunction was documented in the MeHg-exposed group. A dose–response relationship was established between mean maternal hair MeHg levels and performance on the Denver Developmental Screening Test.

A subsequent study evaluated 61 of the original 73 high-dose children, at 6 to 7 years of age, on multiple assessments that included tests of intelligence (WISC-R) and language development (TOLD) (*54*). Results showed that exposed children who scored poorly on the Denver Developmental Screening Test at 4 years of age tended to have decreased scores on the WISC-R intelligence test later in childhood. These neurobehavioral effects were associated with maternal blood MeHg levels of only 20 to 80 ppb.

Elevated levels of blood mercury in women of childbearing age have been found in polar Inuit natives in Northern Greenland (*55*). The Inuits' reliance on whale meat as a dietary mainstay is believed to be the primary source of exposure. Of the women tested, 84% had blood MeHg levels that exceeded the provisional limit set by the WHO (23 ppb). As expected, the fetal levels of MeHg in cord blood (average value of 80.2 ppb) were higher than maternal blood levels (average value of 38.1 ppb). An examination of the relationship between cord blood MeHg and birth weight revealed that decreased birth weights were associated with higher levels of fetal MeHg exposure (*56*). Although information on the neurobehavioral status of these children is not currently available, the cord blood MeHg levels are in the range of values that have been associated with psychomotor retardation (*53*).

Samples of cord blood and maternal hair also were collected and assayed for mercury from women living in the Faroe Islands (*57,58*). With a sample size of 1000 infants, the mean mercury concentration in cord blood was 24.2 ppb, and over 25% of the samples were above 40 ppb. This clearly exceeds the WHO provisional limit for potential health effects and confirms elevated *in utero* MeHg exposure. Faroese children as well as the Inuit children of Northern Greenland should be considered at risk for neurobehavioral alterations associated with *in utero* MeHg exposure.

In summary, a review of the human data on the developmental effects of MeHg exposure indicates that maternal hair levels of 10 to 20 ppm are potentially harmful to

fetal development. This is equivalent to maternal blood levels of 40 to 80 ppb of mercury, assuming a mercury hair-to-blood ratio of 250. To determine a LOAEL, the blood mercury levels must be converted to an estimate of daily consumption (i.e., dose) that would result in the equivalent blood levels. Based on kinetic modeling of MeHg, it is estimated that the long-term daily consumption of 1 µg of mercury will result in blood mercury levels of 1 µg/liter or 1 ppb (*16*). Thus, the consumption of 40 µg of mercury per day would result in a blood mercury level of 40 ppb; which for a 62-kg woman would be equivalent to 0.645 µg/kg/day. If the typically used uncertainty factor of 10 is used to account for sensitive individuals (in this case fetal development), the resulting NOAEL or RfD would be 0.06 µg/kg/day.

## Neurobehavioral Effects in Animals

As discussed above, human exposure to MeHg during prenatal development results in a continuum of effects ranging from blindness, deafness, seizures, abnormal reflexes, and retarded motor development, to far more subtle learning, memory, and psychological effects (*5,9,25,26,47,59*). Adverse effects of MeHg exposure can occur at human brain levels estimated to be as low as 0.3 ppm (*45*).

While animal studies using high levels of MeHg exposure have produced effects similar to those of humans, there have been few efforts to characterize the more subtle effects of low-dose exposure to MeHg during development. Early effects of *in utero* exposure have been documented in nonhuman primate infants. As part of a larger study examining the maternal reproductive and offspring developmental effects of chronic exposure to MeHg, female *Macaca fascicularis* monkeys were exposed to daily doses of MeHg throughout pregnancy (0, 50, 70, or 90 µg/kg/day). Maternal blood MeHg levels averaged 1.28, 1.62, and 2.03 ppm, respectively, for the three treated groups. Maternal blood MeHg levels above 1.5 ppm were associated with a significant decrease in number of viable births (*60*).

During infancy, effects of prenatal exposure were found on measures of cognitive and social development in the offspring of the MeHg-exposed monkeys. *In utero* exposure to MeHg was related to delayed attainment of object permanence (*61*), deficits in visual recognition memory (*62,63*), and abnormal social behavior (*64*). These results, frequently based on test procedures developed for use with human infants, show that *in utero* exposure to MeHg is related to delays in the attainment of important cognitive milestones. The social behavior of the MeHg-exposed infants in established play groups was characterized by a significant decrease in play behavior and an increase in nonsocial behavior. Exposed infants were less likely to engage in species-appropriate play behavior and spent more time alone, distancing themselves from other monkeys in the group. In this same group of animals, a latent effect of prenatal exposure to MeHg indicated puberal growth retardation in exposed males (*49*). Exposed males exhibited significantly decreased weight gain during the juvenile stages of growth (3–5 years of age) but did catch up to the average weight of control males by early adulthood. Subsequent studies in adulthood with these animals have found very slight effects on an intermittent schedule of reinforcement (fixed-interval/fixed-ratio) (*65*). In this group of animals, overall study results do not support long-term deficits in adult learning and memory abilities (*66*). However, preliminary results indicate there may be deficits in adult visual function. Results from this group of monkeys indicate that developmental effects are seen at maternal exposures of 50 µg/kg MeHg/day.

Confirmation of the developmental effects of MeHg exposure is evident from Canadian studies in which monkeys were exposed to MeHg either post- or pre- and postnatally (birth to 7 years of age) at 25 or 50 µg/kg/day. In one study, infants were tested on a fixed-interval operant learning task. Exposed infants showed slight alterations in performance, indicating a possible disruption of time perception (*67*). In the same study, MeHg exposure was not related to learning impairments on discrimination reversal tests. Developmental exposure to MeHg was also shown adversely to affect visual, auditory, and somatosensory function in monkeys (*67–71*). Visual psychophysical studies with these monkeys have shown treatement-related deficits in spatial contrast sensitivity and facilitation of low-luminance temporal contrast sensitivity (*69*). Subsequent studies have described overt sensory-motor deficits (i.e., lack of coordination in exercise cages) and a loss of vibration sensitivity (*70–72*). These effects were observed at the lowest doses tested (25 µg/kg), which is characteristic of many studies with MeHg.

In rodents, one of the most frequent findings related to prenatal MeHg exposure is an increased rate of intrauterine death (*10*). Studies on the developmental effects of MeHg on rats (Table 2) and mice (Table 3) have provided a means of examining specific hypotheses regarding the mechanisms of action of MeHg. These studies also provide information on the levels of maternal exposure at which no adverse effects are observed in the offspring. Typically, pregnant rats or mice were dosed with MeHg for a restricted period of time during gestation. To compensate for the short exposure periods, relatively high doses of MeHg were often used. The most common neurological deficit observed was altered locomotion or exploratory behavior (*73–78*). These findings are consistent with results from high-exposure human studies which revealed significant delays in aspects of motor development such as crawling, standing, and walking. Learning deficits have also been observed following developmental exposure to MeHg (*77–81*).

The most comprehensive study to assess the developmental effects of MeHg in rats was done as part of the Collaborative Behavioral Teratology Study (*78*). In this multilaboratory study, using the same testing protocol, pregnant rats were exposed to either 2 or 6 mg/kg of MeHg on days 6 through 9 of gestation. These studies found dose-related changes in behavior characterized by increased levels of activity and impaired learning of auditory startle habituation in exposed pups. Lower doses of MeHg were not examined, so a NOAEL could not be determined. Two studies have assessed the effects of low-level prenatal exposure to MeHg using schedule-controlled operant behavior (*82,83*). In these studies, rats were dosed with either 0.005, 0.01, 0.05, or 2.0 mg/kg of MeHg during days 6 through 9 of gestation. The offspring were then tested on a differential reinforcement of high rate schedule. This task requires the subject to respond to a lever a specified number of times within a fixed period to receive a reinforcement (e.g., two responses are required within 1 sec). No adverse effects were observed at a dose of 0.005 mg/kg. All other treated groups had reduced success rates. Although no blood or brain mercury levels were reported, it is estimated that the brain Hg levels were as

**Table 2.** Effects of *in utero* MeHg exposure in rats.

| Dose, mg/kg | Exposure | Noted effects | NOAEL | Reference |
|---|---|---|---|---|
| 0.005, 0.01, or 0.05 | GD 6–9 | Differences in DRH operant testing noted in 0.01 and 0.05 dose groups. | 0.005 mg/kg dose group | Bornhausen et al. (*83*) |
| 0, .25, 1.25, 2.50, or 5 | GD 6–15 | No live offspring in 5 mg/kg dose group; 2.5 mg/kg group displayed impairment in all preweaning measures, locomotion, open field and startle response performance; 1.25 mg/kg group showed deficits only in swimming | 0.25 mg/kg dose group | Geyer et al. (*73*) |
| 0, .05, 0.5, or 5 | GD 0, 7, or 14 | No noted differences in litter size, birth weight, gross appearance, or operant behavior | 5 mg/kg dose group | Hughes and Sparber (*101*) |
| 0, .05, or 2.0 | GD 6–9 | Showed dose-dependent decreases in learning using the DRH operant test. No noted differences in general motility or motor coordination | No NOAEL | Musch et al. (*82*) |
| 0, 2 or 6 | GD 6–9 | Auditory startle habituation increased, increased activity measures, alteration in visual discrimination | No NOAEL | Buelke-Sam et al. (*78*) |
| 0 or 8 | GD 8 | Stereotyped sniffing elicited in treated only; no changes in locomotor activity, altered passive avoidance response | No NOAEL | Cuomo et al. (*80*) |
| 0, 5, or 8 | GD 8 or 15 | Decreased maternal weight gain at high dose, decreased neonatal activity, reduced acquisition two-way avoidance | No NOAEL | Eccles and Annau (*81,102*) |
| 0, 2, or 6 | GD 6–9 | Both dose groups showed reduced postweaning figure 8 activity, increased Biel water maze time, errors and proportion of trial failures in addition to delayed developmental growth | No NOAEL | Vorhees (*77*) |
| 0, 10 (IP) | GD 18 | Altered brain cellular arrangement and neuronal migration | No NOAEL | Geelen et al. (*32*) |
| 0 or 5 | GD 7 | Altered visual-evoked potentials | No NOAEL | Dyer et al. (*103*) |
| 0 or 2.5 | Throughout | Altered visual-evoked potentials | No NOAEL | Zenick (*104*) |
| 0 or 2.5 | Throughout | Increased errors in water T-maze; no motor impairment | No NOAEL | Zenick (*105*) |

GD, gestational day(s).

**Table 3.** Effects of *in utero* MeHg exposure in mice.

| Dose, mg/kg | Exposure | Noted effects | NOAEL | Reference |
|---|---|---|---|---|
| 0, 1, 2, 3, 5, or 10 | GD 8 | Effects noted in animals dosed 3.0 mg/kg or higher in two-way shuttle box, active and passive avoidance, litter size, no motor impairment | 2 mg/kg dose group | Hughes and Annau (*106*) |
| 20, 25, or 30 | GD 14, 15, or 16 | Offspring at 25 and 30 mg/kg did not survive; 20 mg/kg group showed neurologic disturbances, righting problems | No NOAEL | Inouye et al. (*74*) |
| 0, 6, 8, or 12 | GD 10 | All dose groups showed decreased exploratory behavior, rearing, urination, and increased backing | No NOAEL | Su and Okita (*75*) |
| 0, 2, 4, or 8 | GD 6–13 | Retarded growth, embryolethal and teratogenic in 129 (when dosed days 9–13), teratogenic in A/J (dosed days 9–13) | No NOAEL | Spyker and Smithberg (*107*) |
| 0 or 8 | GD 7 or 9 | Decreased exploratory behavior, increased backing; demonstrated neuromuscular impairment while swimming | No NOAEL | Spyker et al. (*76*) |

GD, gestational day(s).

low as 0.04 ppm, well below levels thought to produce adverse effects in humans.

In summary, results from monkey studies indicate that a LOAEL for developmental effects is evident at a dose of ~25 µg/kg/day of MeHg. Rodent studies indicate effects may be observed at doses as low as 10 µg/kg/day of MeHg, with effects replicated at 50 µg/kg/day. Using the results from the monkey studies, a NOAEL of 2.5 µg/kg/day is derived using the standard procedure of dividing the LOAEL by a factor of 10. To convert a NOAEL derived from animal studies to one for humans, an uncertainty factor of 10 is typically used to account for interspecies differences. An additional uncertainty factor of 10 is then applied to account for sensitive individuals in the human population. Using a factor of 10 is appropriate given the sensitivity of the developing nervous system to the adverse effects of MeHg. The above risk analysis indicates that a more conservative RfD for MeHg exposure would be 0.025 µg/kg/day, which would provide a level of safety for the developing nervous sytem.

## Neurobehavioral Effects of Other Neurotoxic Compounds

Methylmercury clearly is not the only compound that can adversely affect the developing nervous system. Lead is one of the best studied environmental neurotoxicants and is a good example of the problems associated with understanding the effects of very low levels of exposure (*84–86*). The widespread exposure of children to lead made it possible to perform numerous human epidemiology studies that convincingly demonstrated that low-level exposure is harmful to the developing nervous system (*87*). Animal studies, particularly those in monkeys, confirmed that low-level exposure to lead had adverse developmental effects (*88*). The consequences of the deleterious effects of lead on normal childhood development are just beginning to be examined (*85,89*).

Another important widespread environmental contaminant and neurotoxicant is the lipid-soluble polychlorinated biphenyls (PCBs). This family of over 200 chemicals was used primarily as insulators in electrical equipment. Production of PCBs was banned in the 1970s following recognition of their toxicity and environmental persistence. These lipid-soluble compounds are mobilized during pregnancy, thus exposing the infant *in utero* and are also readily excreted in breast milk during lactation. The neurotoxic effects of *in utero* exposure to PCBs are well documented and have been carefully reviewed (*90–94*). It is

interesting to note that the effects of PCBs appeared to be more related to *in utero* exposure than to postnatal exposure through breast milk.

The voluntary consumption of neurotoxic substances during pregnancy can also result in an array of neurobehavioral effects. Alcohol consumption during pregnancy produces a well-documented syndrome of adverse effects on the nervous system that range from subtle deficits in learning and memory to severe developmental disorders (*95–97*). Animal studies with alcohol have made important contributions to the understanding of fetal alcohol effects and demonstrate the comparability of human and animal findings (*98*). Studies on the long-term impact of prenatal alcohol exposure demonstrate the individual and societal consequences of early neurotoxicant exposure (*95,97,99*). Other drugs such as cocaine also affect nervous system development (*100*).

## Conclusions and Recommendations

Methylmercury is a compound worthy of scientific and societal concern. It is clear that MeHg is a widespread environmental contaminant and a potent neurotoxicant that adversely affects the developing nervous system. Mercury continues to be released into the environment by both natural and human-generated sources. It is readily converted to MeHg and accumulates in the food supply, primarily in fish and marine mammals. MeHg is readily absorbed and distributed throughout the body, including the brain and the fetus. Fetal exposure appears to be at a level that is greater than maternal blood levels. Studies of humans exposed to elevated levels of MeHg clearly demonstrate its neurotoxic potential. Animal studies using rodents and nonhuman primates have confirmed the neurotoxic potential of MeHg. However, research into cellular and molecular mechanisms has yet to produce an understanding of MeHg sufficient to allow accurate prediction of its neurotoxicity. Furthermore, human and animal studies on the neurobehavioral effects of developmental MeHg exposure have not determined a level of exposure that is convincingly harmless to the developing fetus.

In many ways, our understanding of the neurotoxic potential of MeHg is similar to that of lead 20 years ago; MeHg is a known neurotoxicant at high levels of exposure but there is little understanding of its effects at lower levels of exposure. The failure to adequately characterize the functional effects of low-level MeHg exposure has compromised the formulation of a sound policy regarding the safe levels of MeHg exposure, particularly for pregnant women or women of child-bearing age. Examination of the results of human studies on the effects of MeHg indicate that maternal hair levels of 10 to 20 ppm may result in adverse effects on fetal outcome. Making the appropriate assumptions and calculations, a level of exposure not expected to be hazardous (RfD) would be 0.06 μg/kg/day. Evaluation of results from animal studies on the developmental effects of MeHg provided an estimated RfD of 0.025 μg/kg/day. The human and animal RfDs are in very good agreement.

Given the current state of knowledge with regard to MeHg exposure, the following recommendations are offered:

- reduce environmental release of all forms of mercury;
- consider restricting the global production and sale of mercury;
- strongly advise pregnant women and women of child bearing age to limit their exposure to sources of MeHg;
- establish an RfD (reference dose) for MeHg of 0.025 to 0.06 μg/kg/day;
- continue research to determine a level of MeHg exposure that would not harm the developing nervous system;
- continue research to understand the underlying molecular mechanisms of action of MeHg;
- assess the long-term neurodegenerative effects of developmental MeHg exposure.

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